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Infantile Epileptic Encephalopathy, Transient Choreoathetotic Movements, and Hypersomnia due to a De Novo Missense Mutation in the *SCN2A* Gene

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Abstract

Mutations of the *SCN2A* gene have originally been described in association with benign familial neonatal-infantile seizures (BFNIS). Recently, single patients with more severe phenotypes and persisting epileptic encephalopathies have been recognized. We report the case of a girl with severe infantile onset epileptic encephalopathy and a de novo missense mutation in the *SCN2A* gene (c.4025T > C/ = ; p.L1342P/ =), who presented with a transient choreatic movement disorder, hypersomnia, and progressive brain atrophy. Whole exome sequencing did not reveal any other disease causing mutation. Our patient contributes to the expanding phenotypic spectrum of *SCN2A*-related disorders and underlines the importance of genetic workup in epileptic encephalopathies.

Keywords
- intellectual disability
- choreoathetosis
- voltage-gated sodium channel
- seizures

Introduction

Infantile onset epileptic encephalopathies often present with intractable seizures, cognitive, behavioral, and neurological deficits and usually have a poor prognosis. The number of monogenic disorders that cause epileptic encephalopathies and the phenotypic spectrum of diverse monogenic epilepsies are rapidly expanding. Driven by a candidate gene approach an increasing number of channelopathies has been related to genetic epilepsies. Voltage-gated sodium channels initiate action potentials in nerve, muscle, and other excitable cells and are essential for normal neuronal firing. Mutations in the various voltage-gated sodium channels cause a broad spectrum of disorders with predominant paroxysmal features such as epilepsy, hemiplegic migraine, periodic paralysis, or cardiac conduction defects. Well-known phenotypes associated with mutations in the *SCN1A* gene may lead to severe myoclonic epilepsy of infancy and genetic epilepsy with febrile seizures plus. Mutations in the *SCN2A* gene were originally described with benign familial-neonatal infantile seizures (BFNIS).[1] Over recent years, the spectrum of *SCN2A* mutations has widened markedly[2,3] with descriptions of some severely affected patients. We report on a girl with a de novo *SCN2A* mutation presenting with intractable seizures, primary global developmental impairment, and additional features such

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as choreoathetotic movements, hypersomnia, and progressive brain atrophy.

Case Report

The girl is the first child of a healthy Japanese mother and a European father who had benign focal childhood epilepsy with centrotemporal spikes. The patient was delivered by caesarean section after an uneventful pregnancy. Her Apgar scores were 7/9/10, head circumference was 36 cm (percentile: 50–75), body length 48 cm (percentile: 3), weight 2,970 g (percentile: 3–10); physical appearance was normal. Early development was remarkable due to feeding problems, rare smiling, and lack of visual contact. At the age of 5 months, she was referred to our neuropediatric outpatient clinic by an ophthalmologist, who suspected infantile spasms because of abnormal eye movements. The girl presented with severe truncal hypotonia, choreoathetotic movements predominantly of the upper extremities and the face. Electroencephalography (EEG) revealed hypsarrhythmia accentuated over the left hemisphere and short bursts of β rhythms. Short tonic seizures occurred with brisk stretching of the right arm, flexion of the left arm, gaze deviation to the left, and narrowing of the left palpebral fissure, occasionally associated with a facial flush (►**Video 1**). Ictal EEG showed pronounced slowing, amplitude suppression over the right hemisphere, and multifocal sharp wave activity. Pyridoxine was ineffective but seizures were initially controlled by vigabatrin. Because of persisting hypsarrhythmia prednisolone (4 × 10 mg) was administered over 4 weeks and lead to resolution of hypsarrhythmia. Hypsarrhythmia and seizures relapsed 4 weeks after steroid withdrawal and since then seizures remained therapy resistant to topiramate, lamotrigine, phenobarbital, valproic acid, levetiracetam, clobazam, sultiame, and a 2.5:1 ketogenic diet. At the age of 1 year and 9 months, tonic seizures were associated with left hemispheric rhythmic theta activity and simultaneous right hemispheric rhythmic sharp waves followed by suppression on EEG (►**Fig. 1**). Over the years, different seizure types evolved, mainly generalized and focal tonic seizures as well as serial myoclonic jerks. Head circumference dropped below the third percentile by the age of 6 months. During infancy, the mother reported prolonged sleeping up to 22 hours per day independent of the anticonvulsive drugs administered and the child had to be awakened for regular feeds. In polysomnography sleep cycles were poorly depicted and hypersomnia could not be quantified due to continuous predominant delta activity and absent spindles and K-complexes. The choreoathetotic movements decreased from the age of 12 months, but daytime sleepiness persisted. At the age of 4 years, her head circumference was 46 cm, −4.0 standard deviation scores; length and weight were on the third percentile. She was still having approximately 10 seizures per day. Visual contact was absent, spontaneous movements were rare and undirected; she had profound hypotonia with head lag and brisk reflexes with an exhaustible ankle clonus.

Video 1

Choreoathetotic movements and short tonic seizure. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1372302.

Cranial magnetic resonance imaging at age 5 months and 2.5 years revealed a progressive cortical and subcortical atrophy and a minor cerebellar atrophy. Proton magnetic resonance spectroscopy of the basal ganglia and white matter showed normal metabolites. Extended metabolic workup revealed normal plasma amino acids, acylcarnitines, sialotransferrin isoelectric focusing, pipecolic acid, homocysteine,

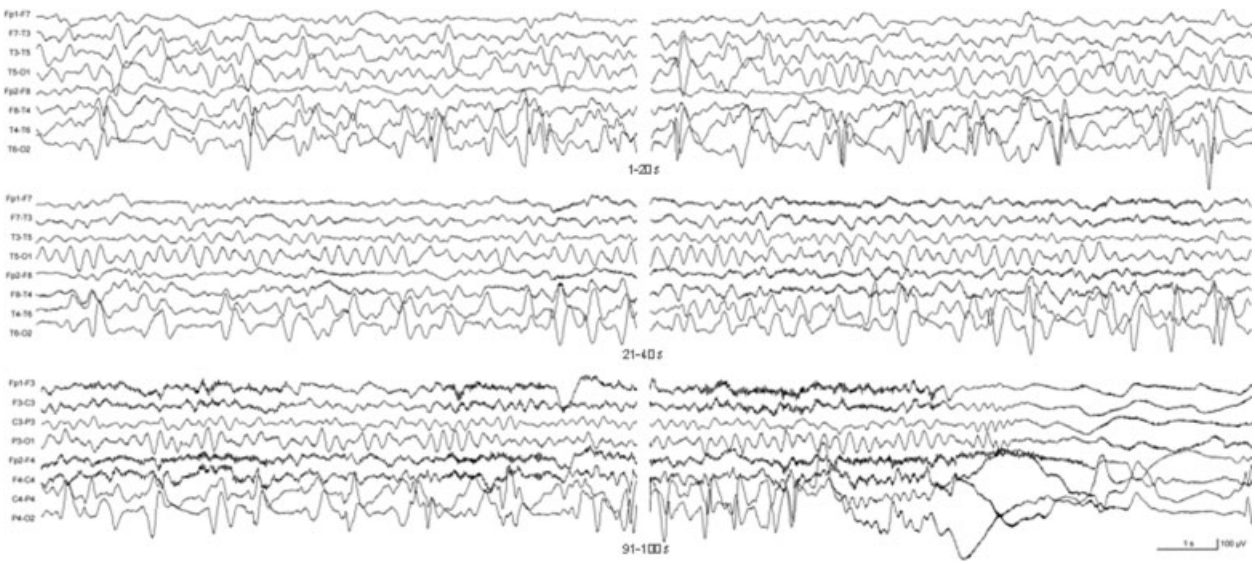

Fig. 1 Focal seizure pattern (electroencephalography) at the age of 1 year and 9 months. Evolution of rhythmic left hemispheric theta activity, meanwhile rhythmic sharp over the right temporo-occipital region followed by generalized suppression.

and guanidinoacetate. CSF lactate, biogenic amines, folate, pterins, and amino acids, as well as the CSF to blood glucose ratio were all normal, as were organic acids in urine. The karyotype was 46,XX; high-resolution chromosomal microarray analysis using an Affymetrix cytogenetics 2.7 array revealed only common copy number polymorphisms. At the age of 4 years, targeted Sanger sequencing of the *SCN2A* gene was performed because it was recently found to represent one of the most common causes of unexplained severe intellectual disability[4] and lead to the detection of a heterozygous missense mutation (c.4025T > C/ = ; p.L1342P/ =), which was absent in both parents. Pathogenicity of this mutation is supported by its de novo occurrence, exchange of a highly conserved amino acid, and mutation modeling. Transmembrane helices in *SCN2A* were predicted using the programs TmHMM,[5] TMpred, and Toppred.[6] The topology of the transmembrane helix and the effect of the mutation were modeled with Sybyl7 (Tripos Inc., St Louis, Missouri, United States). RASMOL[7] was used for visualization. All three tools independently predict that L1342 is located in a transmembrane helix of *SCN2A*. These methods additionally list scores, which are a measure for the helix forming propensity of the respective sequence stretch. As indicated by the scores, a replacement of L1342 by proline decreases the helix propensity suggesting that the helix is less stable in the mutant (►**Fig. 2**). A deleterious or damaging effect was also highly supported by PolyPhen2 (1.0000), SIFT (D), LRT (0.0003), MutationTaster (0.9956), MutationAssessor (5.02), and PhyloP (1.78) in silico analysis. The c.4025T > C mutation was previously unreported including the data from the 1,000 genome project and the 6,500 exomes of the National Heart, Lung, and Blood Institute. Considering the possibility of an independent, nonallelic second mutation as a modifier of the phenotype, we performed whole exome sequencing of the patient and both parents using a SOLID 5500 XL device (Carlsbad, California, United States) and the Agilent SureSelect Human All Exon V5 capturing system (Agilent, Santa Clara, California, United States) with a 65 forward/30 reverse read length and an average read depth of 146 ×. Trio data were analyzed for de novo and homozygous or compound heterozygous rare variants. In addition to the previously identified *SCN2A* mutation, three additional de novo heterozygous mutations were observed, all of which were predicted to be benign by the various in silico tools and occurred in genes with no known disease association (*FAM75A4* c.676G > A, p.D226N; *TMEM55B* c.289C > T, p.L97F; *SLFN11* c.1691T > A, p.L564H). Likewise, compound heterozygous variants in the genes *ANKRD35* and *TRIML2* with unknown function and in the *OTOG* gene causing autosomal recessive nonsyndromic hearing loss were predicted to be benign. Only the compound heterozygous variants (rs139476696 — minor allel frequency of 0.0005 — and rs144054131 — minor allel frequency of 0.0023) identified in the *PPARGC1B* gene reached a medium score of pathogenicity, but neither a disease association with these specific SNPs nor an autosomal recessive disease has yet been assigned to the encoded peroxisome proliferator-activated receptor gamma, co-activator 1β (also known as ERRL1, PERC, PGC-1(β), and PGC1B). After detection of the mutation, carbamazepine was introduced leading to a significant increase in seizure frequency and therefore discontinuation after a few days.

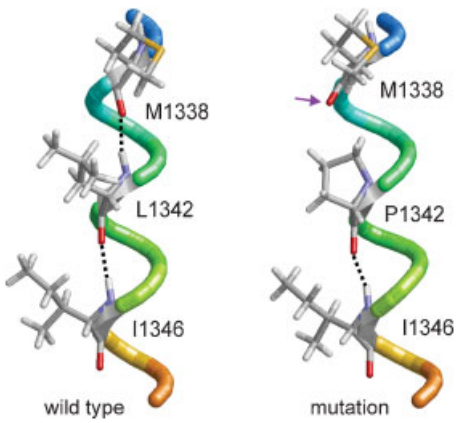

Fig. 2 Structure of residues 1,336 (blue tube) to 1,349 (orange tube) of the *SCN2A* transmembrane helix. The wild type and L1342P mutant are shown in the left and right panel, respectively. Residues 1,338, 1,342, and 1,346 are shown in stick presentation and backbone hydrogen bonds are indicated as black dotted lines. Because of the lack of an amide proton, P1342 cannot form a hydrogen bond with M1338, which is predicted to lead to a destabilization of the helix and a rearrangement of M1338 (magenta arrow). In addition, the bulky ring of the proline causes a rearrangement of the M1338 backbone suggesting that the mutation affects both the stability and geometry of the transmembrane helix.

Discussion

Mutations of the sodium channel subunit gene *SCN2A* have initially been described in several families with BFNIS.[1] BFNIS is characterized by sudden neonatal infantile onset of seizures with remission in infancy and normal development. In recent years, the clinical spectrum of *SCN2A* mutations has expanded considerably. Our patient presented with marked developmental delay before the detection of hypsarrhythmia and the onset of tonic seizures at the age of 5 months. Over time, seizure patterns became more variable and remained pharmacoresistant as described in other patients with the severe phenotype of *SCN2A*-related encephalopathy. Our patient showed some additional distinct features. Notably, the continuous choreatic movements were impressive during infancy and preceded the onset of epilepsy. Chorea and ballism associated with infantile spasms, severe developmental delay, and cerebral atrophy have yet been described in one girl with a de novo *SCN2A* mutation.[2] Interestingly, hypermotoric movement disorders can occur along other infantile epilepsies as choreo–ballistic movements associated with guanidionoacetate methyltransferase deficiency[8] and *STXBP1* mutations[9] or paroxysmal kinesigenic dyskinesia with *PRRT2*-related infantile convulsions.[10] While choreatic movements in *PRRT2* are described as paroxysmal our patient had constant choreoathetotic movements that were only interrupted by sleep but subsided beyond infancy without specific treatment.

Hypersomnia has so far not been reported in cases with *SCN2A* mutations. Though excessive daytime sleep was evident in our patient, this could not be proven by polysomnography as sleep-specific patterns were absent. Voltage-gated

sodium channels seem to play an important role in sleep homeostasis as demonstrated in mouse models in *SCN1A* and *SCN8A* mutations. The mutant mice developed altered sleep regulation with sleep deficit in *SCN1A* and reduced wakefulness in *SCN8A* mutations.[11] Cerebral atrophy, as observed in our patient, has been reported in severe cases of epileptic encephalopathies including *SCN1A* and *SCN2A* mutations.[2]

Almost all *SCN2A* mutations are missense as in our patient. Functional consequences range from gain-to-loss-of-function of the Nav1.2 channel. Thus, characterization of the impact of individual mutations on channel function could well influence the choice of anticonvulsant drugs. In general, it seems that channel properties are altered to a greater extent in patients with intractable epilepsies.[3] The p.L1342P mutation observed in our patient affects one of the six transmembrane segments of domain III of the Nav1.2 channel and is predicted to result in destabilization of the protein. We tried carbamazepine in our patient because many reported *SCN2A* mutations result in a gain of function of the Nav1.2 channel. Unfortunately, we saw an increase in seizure frequency so it can be hypothesized that her mutation rather leads to a loss of function.

In a recent study, *SCN2A* missense mutations were detected in 15 of 328 patients with early onset epileptic encephalopathies.[2] Nine of the described cases were classified as Ohtahara syndrome.

Another study identified mutations in the *SCN2A* gene as one of the most common causes of unexplained, isolated severe intellectual disability by whole exome sequencing.[4] This questions the selective impact of epileptiform activity on the cognitive abilities of children with *SCN2A* mutations and the definition of epileptic encephalopathy per se.

In our patient, the co-occurrence of severe global developmental impairment, intractable epilepsy, and a transient movement disorder led to the suspicion of a monogenic disorder and to sequencing of the *SCN2A* gene as the first of several possible candidate genes.

Acknowledgment

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References

1 Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. Lancet 2002; 360(9336):851–852
2 Nakamura K, Kato M, Osaka H, et al. Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome. Neurology 2013; 81(11):992–998
3 Shi X, Yasumoto S, Kurahashi H, et al. Clinical spectrum of SCN2A mutations. Brain Dev 2012;34(7):541–545
4 Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012;380(9854): 1674–1682
5 Sonnhammer EL, von Heijne G, Krogh A. A hidden Markov model for predicting transmembrane helices in protein sequences. Proc Int Conf Intell Syst Mol Biol 1998;6:175–182
6 Claros MG, von Heijne G. TopPred II: an improved software for membrane protein structure predictions. Comput Appl Biosci 1994;10(6):685–686
7 Sayle RA, Milner-White EJ. RASMOL: biomolecular graphics for all. Trends Biochem Sci 1995;20(9):374–376
8 Leuzzi V, Mastrangelo M, Battini R, Cioni G. Inborn errors of creatine metabolism and epilepsy. Epilepsia 2013;54(2):217–227
9 Kanazawa K, Kumada S, Kato M, Saitsu H, Kurihara E, Matsumoto N. Choreo-ballistic movements in a case carrying a missense mutation in syntaxin binding protein 1 gene. Mov Disord 2010; 25(13):2265–2267
10 Wang JL, Cao L, Li XH, et al. Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. Brain 2011;134(Pt 12):3493–3501
11 Papale LA, Makinson CD, Christopher Ehlen J, et al. Altered sleep regulation in a mouse model of SCN1A-derived genetic epilepsy with febrile seizures plus (GEFS+). Epilepsia 2013;54(4):625–634